Systemic Mastocytosis: Retrospective Review of a Decade's Clinical Experience at the Brigham and Women's Hospital

Richard F. Horan and K. Frank Austen

Department of Rheumatology and Immunology, Brigham and Women's Hospital; and the Departments of Dermatology and Medicine, Harvard Medical School, Boston, Massachusetts, U.S.A.

The clinical experience with a group of 21 patients with systemic mastocytosis followed at our institution is summarized. Cutaneous and gastrointestinal symptoms and findings were the most prominent chronic manifestations; episodic vascular collapse was the most dramatic acute event. All patients had indolent mastocytosis. There was no mortality. *J Invest Dermatol 96:5S–14S, 1991*

The diagnosis of systemic mastocytosis is based on a suggestive clinical history, a tissue diagnosis of mast cell hyperplasia, and supportive evidence derived from physical examination or laboratory investigation. The factors that eventuate in mast cell proliferation in affected individuals are unknown and may conceivably vary among patients. Symptoms appear to derive primarily from the systemic and local effects of mast cell–derived mediators and only secondarily from the space-occupying nature of the mast cell infiltrate. The natural history of systemic mastocytosis was also poorly defined until recently, when interest in the prognosis and classification of patients with this condition increased [1]. This report is intended to present, albeit in retrospect and in uncontrolled fashion, a decade's experience with systemic mastocytosis at the Brigham and Women's Hospital.

METHODS

We reviewed the records of all the patients (n = 40) with a diagnosis of mastocytosis who were seen in the Asthma and Allergic Diseases Center (previously the Ambulatory Immunology Center) of the Brigham and Women's Hospital (previously Robert B. Brigham Hospital) for consultation or continuing care between January 1, 1980, and June 1, 1990. Twenty-one had systemic mastocytosis according to three defining criteria: 1) history; 2) biopsy findings diagnostic of mastocytosis from at least one tissue site; and 3) elevated measurement of 24-h urine histamine or N-methylhistamine, biopsy findings diagnostic of mastocytosis from a second tissue, or persistent hepatosplenomegaly unexplained by other clinical processes. The presence of cutaneous mastocytosis for which there was no evidence of systemic involvement or the lack of data necessary to reach a conclusion by the defining criteria excluded 19 other patients. We analyzed the clinical data contained in the hospital records (and outside records as available) of the 21 patients with clear-cut mastocytosis.

Reprint requests to: Dr. Richard F. Horan, Department of Rheumatology and Immunology, Brigham and Women's Hospital, Boston, MA 02115.

Abbreviations:
CNS: central nervous system
CT: computed tomography
EEG: electroencephalogram
GGT: gamma glutamyl transferase
GI: gastrointestinal
GM-CSF: granulocyte macrophage–colony-stimulating factor
GOT: glutamic oxalic transaminase
GPT: glutamic pyruvic transaminase
Ig: immunoglobulin
IL: interleukin
PUVA: 8-methoxypsoralen plus ultraviolet A
TMEP: telangiectasia macularis eruptiva perstans
UP: urticaria pigmentosa

RESULTS

Characteristics of Patient Group At the close of the review period, ages of patients ranged from 21 to 88 years, with a mean of 57; reported age at onset of initial symptom ranged from 7 to 69 years, with a mean of 37. Male to female ratio was 1 : 3.2. In almost all individuals, the initial recalled manifestation of the illness was a cutaneous eruption. Duration of illness from initial symptomatic manifestation to close of the review period ranged from 5 to 55 years, with a mean of 20.5. The interval between onset of initial symptoms and the diagnosis of any form of mastocytosis (whether urticaria pigmentosa, some other form of cutaneous mastocytosis, or systemic mastocytosis) ranged from virtually immediate to 35 years, with a mean of 9.5. Follow-up at this institution ranged from less than 1 year to 15 years, with a mean of 5.9. Seventeen patients had been seen for most recent follow-up within the past year; 19 had been seen by one or both of us. There has been no mortality.

Referral to our center had been made by practitioners of various medical specialties, most commonly general internists (Table I).

Additional medical illnesses or problems affecting patients are listed in Table II. One patient, who also had asthma, had a definite history of seasonal allergic rhinitis; however, there appeared to be no increased personal or family history of atopy for the group as a whole. There was no known family history of mastocytosis.

Clinical Presentation Episodic flushing, ranging from mild to severe, was the most frequently noted complaint and was described by 20 of the 21 patients in the group. Nineteen patients reported frequent headaches, which they described as bilateral and pounding, often severe, and sometimes associated with flushing and nausea. Episodes of vascular collapse with syncope or near syncope were reported by eight patients, six of whom had documented hypotension at the time of attack. Six patients reported palpitations (described as a rapid or racing heartbeat) during severe systemic flares.

Two patients noted mild wheezing in association with significant episodic exacerbation of their illness, although wheezing only

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Table I. Specialties of Referring Physicians[a]

Specialty	Patients (number)
General internists	8
Dermatologists	6
Gastroenterologists	2
Allergist	1
Neurologist	1
Endocrinologist	1
Self	2
Unknown	1

[a] Total sums to 22 because one referring physician practiced dermatology and allergy concurrently.

rarely accompanied attacks. One had baseline asthmatic bronchitis felt to be due to long-time use of cigarettes. No patients reported upper respiratory obstruction.

Twelve patients complained of rhinitis, usually mild and perennial, with symptoms of nasal congestion and rhinorrhea; 17 described pruritus, most commonly mild; and 15 reported urtication, generally mild and localized.

Seventeen patients complained of bouts of significant abdominal pain. Consistent with other reports [2], our patients described two general varieties of abdominal pain: dyspeptic pain and non-dyspeptic, crampy, colicky abdominal discomfort. Most patients reported both varieties of pain. Although both types were episodic, the crampy variety was more likely to occur in waves of exacerbation and remission, with flares lasting from several hours to several days, occasionally as long as a week. Flares of non-dyspeptic pain were associated with ingestion of alcohol, ingestion of various foods (variable from patient to patient, and at least in some cases depending on method of preparation, condiments, and temperature), stress, and concurrent level of general disease activity. Two patients had diagnoses of peptic ulcer disease and three others had esophagitis, gastritis, or duodenitis, all meeting endoscopic or roentgenographic criteria. One of these patients required esophageal dilatation because of distal esophageal stricture due to esophagitis. Two patients experienced episodes of upper gastrointestinal bleeding from severe gastritis/duodenitis. Most of the other patients reporting abdominal pain had clinical complaints, either intermittent or persistent, suggestive of at least some degree of esophagitis, gastritis, or duodenitis. Twelve patients complained of episodes of nausea, occasionally associated with vomiting, commonly but not consistently associated with abdominal pain. Fourteen patients reported diarrhea or increased frequency of bowel movements (multiple loose or semiformed stools per day). One patient, who had extensive mastocytosis involvement of small bowel and colon and evidence of portal hypertension, had hematochesia on one occasion. Extensive roentgenographic and colonoscopic evaluation revealed no apparent etiology except for the possibility of a hemorrhoidal bleed. There were no reports of melena in the absence of active peptic ulcer disease or gastritis/duodenitis. Five patients had evidence of malabsorption, with abnormal d-xylose tests and/or notably reduced serum carotene levels noted in four; the other had a low folate level and hypogammaglobulinemia in the setting of a normal diet and histologic and roentgenographic evidence of profound mucosal involvement of the small bowel. Three of the five had symptoms and examinations suggestive of peripheral polyneuropathy, which the neurologic consultants described as most likely due to nutritional deficiency.

Sixteen patients described a constellation of psychologic difficulties, with irritability, poor concentration, and poor short-term memory as key features. Fifteen of 20 described intolerance to ingested ethanol, with pronounced flushing and, usually, precipitation of abdominal pain. Three patients related histories of adverse reactions to aspirin: two described onset of flushing after aspirin ingestion, and one related angioedema to aspirin use. Six patients in our population, including two of those with a history of vascular collapse, were on beta-blockers at some point during the study period; review of their histories elicited no evidence of specific adverse reaction to beta blockade.

Two patients complained of well-localized bone pain. Fever did not manifest as a feature of mastocytosis in our patient group. Several patients complained of moderate fatigue. Anorexia was reported only as an accompaniment of exacerbations of gastrointestinal complaints and was otherwise not a problem.

Physical Findings Cutaneous manifestations were the most prevalent abnormality on physical examination. Three patients had no apparent cutaneous lesions. Seventeen patients had urticaria pigmentosa, characterized by the presence of multiple red-brown papules and plaques, sometimes coalescent, and generally symmetrically distributed. Lesions consistently involved the trunk and extremities but spared the face. In many patients with urticaria pigmentosa lesions of long standing, the lesions had a mild telangiectatic component. In four patients, the lesions of urticaria pigmentosa gradually faded, with complete or near-complete resolution and no residue except for occasional faint hyperpigmented macules; duration of illness in those patients ranged from 19 to 55 years with a mean of 35. The fading of the lesions was not accompanied by remission of systemic symptoms; all four had prominent extracutaneous manifestations of their disease. One patient, age 21 years, had telangiectasia macularis eruptiva perstans, with prominent telangiectatic mats on a reddish-brown macular background over trunk and extremities. One patient, who had portal hypertension, developed prominent spider telangiectases (different from the telangiectatic mats of telegiectasias macularis eruptiva perstans, which are characterized by the absence of a central feeding vessel and the presence of a red-brown macular background).

Persistent hepatomegaly with a firm, although not rock hard, liver edge and minimal to mild tenderness was noted during the clinical course of eight patients and splenomegaly in four. Peripheral lymphadenopathy was not apparent on physical examination of any patient in the series.

Laboratory Findings Routine laboratory evaluation revealed a mild leukocytosis, to approximately 13,500/mm^3, in one patient,

Table II. Coexisting Diagnoses in Patients with Systemic Mastocytosis

Diagnosis	Patients (number)
Hypertension	5
Ischemic heart disease with angina pectoris	4
Diverticulitis	4
Mitral valve prolapse	3 (all female)
Autoimmune thyroiditis	2
Adult-onset diabetes mellitus	2
History of bone fracture	4
Spinal stenosis	1
Osteogenesis imperfecta	1
Osgood-Schlatter syndrome	1
Cerebrovascular accident, lacunar type, in the setting of hypertension	1
Hypertriglyceridemia, probably familial	1
Pancreatitis, cause unknown (not the patient with hypertriglyceridemia)	1
Asthma	1
Chronic obstructive pulmonary disease in the setting of long-standing cigarette use	1
Anaphylaxis Associated with hymenoptera envenomation	1
History of malignancy (excluding nonmelanoma skin cancer)	2
Breast cancer	1
Breast cancer and melanoma	1
Chromophobe adenoma	1

who had noteworthy systemic symptoms, documented bone marrow involvement, and long-standing pronounced eosinophilia. Another patient has had intermittent mild leukopenia (approximately 2,400 to 3,000/mm³ with normal values at baseline) and a course notable for marked symptoms involving skin and gastrointestinal tract, portal hypertension, splenomegaly, malabsorption, and bone-marrow involvement (with adequate cellularity and numbers of precursors of each cell line and without evidence of hematologic dyscrasia). Five patients, who are clinically indistinguishable from the rest of the group, have had eosinophilia (1,300 to 6,000/mm³), of long standing, preceding or coincident with the diagnosis of mastocytosis and having a tendency toward a gradual increase in the absolute eosinophil count. No increase in basophil numbers has been appreciated on peripheral blood smears. Three of four patients with anemia have had mild to moderate anemia, with hematocrits in the range of 30 to 36%; the fourth has had hematocrits as low as 20% (in the setting of nutritional deficiency, portal hypertension, splenomegaly, and a lower gastrointestinal (GI) bleed of unknown etiology). Two patients have had a moderate thrombocytosis, in no instance greater than 650,000/mm³. Thrombocytopenia has not been noted, and accelerated erythrocyte sedimentation rate has not appeared to be a feature of mastocytosis.

Routine chemistries have revealed no abnormalities of blood urea nitrogen or serum creatinine, and serum calcium, phosphorus, and magnesium have been remarkable in only one patient, who had severe malabsorption, hypoalbuminemia, and diminished total serum calcium and magnesium but appropriate values relative to serum albumin. Serum alkaline phosphatase levels have been modestly elevated (slightly above to about 1.5 times the upper limit of normal) in 10 patients and severely elevated (4 times the upper limit of normal) in one, who had severe malabsorption and secondary metabolic bone disease. In most patients with elevated serum alkaline phosphatase levels, liver and bone may both have been contributing to the elevation. Five also had mild to moderate elevations of serum GOT, GPT, or GGT.

Serum protein electrophoresis had been performed within the past 2 years in 16 patients, and in 14 the results were unremarkable. Two (age 73 and 82 years, with symptom durations of 9 and 42 years, respectively) had small IgG(k) monoclonal spikes. On complete examination, including bone marrow aspirate and biopsy, neither had any evidence of myeloma or other hematologic malignancy.

Urinalyses were normal in all patients, except for occasional positive bacterial cultures associated with infection.

Results of histamine assays in 24-h urine collections were available for 20 patients, primarily from the latter two thirds of the review period. All had at least one abnormally elevated measurement, and overall 43 of the 65 available measurements revealed elevated values. For a given patient, greater degrees of elevation tended to occur during periods of significant clinical exacerbation, but this was not a uniform finding. Individual rates of elevated results ranged from one of eight tests to six of six. Measurements of 24-h urine histamine content did not seem strongly predictive of the clinical severity of the disease in this small group. Nine measurements of 24-h urine N-methylhistamine content were available for seven patients; seven samples from six patients contained elevated levels. One patient had a value within the normal range on the sole test performed, and one had an elevated value on one of two measurements. Plasma histamine levels were measured on one occasion in each of two patients and were elevated in both.

Histopathology Skin biopsies in the 17 patients with urticaria pigmentosa revealed mast cell infiltrates in the dermis. The findings on microscopic examination generally were more striking in patients with more confluent and infiltrated lesions. The mast cell infiltrates in macular and less substantive papular lesions were primarily perivascular in location, whereas more substantive lesions showed more extensive intervascular as well as perivascular mast cell infiltrates, with involvement of deep dermis and occasionally even subcutis. The mast cells in the infiltrates all appeared cytologically banal. Biopsies from the patient with telangiectasia macularis eruptiva perstans showed prominent vascular dilatation, as well as an abnormal perivascular mast cell infiltrate. Three of our patients had no clinically evident cutaneous lesions, and skin biopsies of two revealed no significant increase in mast cell numbers; however, those of the third disclosed a striking mast cell infiltrate.

Data from both bone-marrow aspirates and trephine core biopsies were available for 11 patients, aspirates only for two, and trephine core biopsies only for two. Of the 13 patients in whom trephine core biopsies had been done, classic focal paratrabecular mast cell aggregates were appreciated in nine (including both patients for whom biopsy data only were available). In two other patients, aspirates revealed markedly increased mast cell numbers, although classic nodular aggregates were not seen on the corresponding biopsies. Both aspirate and biopsy were negative in two patients with classic cutaneous and systemic symptoms, organomegaly, and/or radiographic evidence of bony involvement; in both, the aspirate and biopsy had been performed elsewhere, using standard decalcification and embedding techniques.

In several cases recently evaluated, plastic-embedded sections that had been prepared for research purposes were available for comparison with the routinely processed slides prepared for diagnostic pathology by standard decalcification and paraffin-embedding techniques. Sections prepared by plastic embedding revealed significantly greater preservation of mast cell granules, enhancing recognition of tissue mast cells. Indeed, two patients with negative or equivocal findings on routinely processed bone-marrow biopsy specimens demonstrated classic, nodular, paratrabecular mast cell aggregates on review of plastic-embedded sections. Marrows of the two patients for whom aspirates only were available had no apparent increase in mast cell numbers, but both had diagnostic histopathology at one or more extracutaneous sites, and one had been reported to have a diagnostic bone-marrow biopsy elsewhere.

Nodular mast cell aggregates, when seen, were paratrabecular in location. They were non-uniformly distributed, and findings ranged from scattered aggregates to near confluency. Diffuse mast cell hyperplasia was not appreciated in any biopsy specimen. Scattered lymphocytes and, sometimes, eosinophils were associated with the nodular aggregates. A background eosinophilia was noted in specimens from several patients without peripheral eosinophilia as well as the five with significant peripheral eosinophilia. Involved bone-marrow biopsy specimens showed focal and diffuse fibrosis, ranging from mild to marked. Specimens generally were normocellular, ranging from mild hypocellularity to mild hypercellularity. All hematopoietic cell lines were present without significant abnormality. As in skin, the mast cells were cytologically banal.

Liver biopsies of the two patients in which this procedure was performed did not reveal findings suggestive of mastocytosis. In one, the histology revealed rare, scattered mast cells but more significant was evidence of chronic active hepatitis and early cirrhosis that seemed to be attributable to transfusion-associated non-A, non-B hepatitis. Fatty change in the other patient's biopsy was attributable to probable familial hypertriglyceridemia. No specimens of spleen or lymph node were available for histologic examination. Four patients had small bowel biopsies and two had colon biopsies, all with findings felt to be consistent with their diagnoses of systemic mastocytosis.

Radiographic Findings Seven of the bone scans performed in 18 patients were considered normal or had findings consistent with degenerative arthritis or some other known process not related to the patient's mastocytosis. Three scans revealed unifocal abnormalities thought secondary to mastocytosis, and seven revealed multifocal abnormalities. One other patient, who had long-standing mastocytosis and malabsorption with secondary metabolic bone disease, had a "superscan."

Plain films commonly showed a combination of osteopenic, lytic, and sclerotic changes, as have been described in the literature. Plain films of various types (e.g., chest films or scout films for gastrointestinal studies) commonly showed diffuse osteopenia without other

abnormality. Upper GI series with small bowel follow through demonstrated mucosal thickening, nodularity, or polypoid defects felt to be consistent with mastocytosis in eight patients and were negative in six. Barium enemas of five patients showed mucosal thickening felt to be due to mastocytosis involvement of bowel wall in only one patient.

Computerized tomography of the abdomen, abdominal ultrasound, and liver/spleen scans provided confirmation of clinical findings of hepatosplenomegaly. In one patient, CT scan revealed mild mesenteric lymphadenopathy, which has remained stable for approximately 3 years without evidence of evolving lymphoproliferative illness. Cerebral magnetic resonance imaging and cranial CT scan in four patients each demonstrated no specific findings.

Neurologic and Psychologic Studies Electroencephalography was performed in a prospective study on 14 patients; five studies were normal, nine revealed nonspecific abnormalities thought to be consistent with toxic or metabolic process, and none showed seizure activity.

Results of psychiatric interviews and a battery of psychologic tests have been detailed in a previous report on 10 patients [3], including seven from the current series. Of the 10 members of the present series so far evaluated in this fashion, nine have a consistent pattern of cognitive difficulties, including diminished attention and memory, and affective changes of anger, irritability, and depression.

Treatment A total of 17 patients were managed at some point with a combination of H1 and H2 antagonists, and four were treated with H1 antagonists alone. H1 antagonists appeared to relieve cutaneous manifestations of pruritus and urtication, as well as flushing, headache, and rhinitis. In addition, they appeared to relieve abdominal pain, particularly the non-dyspeptic variety, and provide some amelioration of cognitive and affective symptoms. H2 antagonists reduced dyspeptic symptoms and seemed as well to be of slight benefit adjunctively in the relief of symptoms for which H1 antagonists provided a pronounced benefit. The specific antihistamines and combinations used varied from patient to patient and from time to time in a given patient. None of the commonly used agents showed a definite advantage over others at comparable doses. The non-sedating agents astemizole and terfenadine were helpful in selected patients, but they were not widely enough used in this series of patients to justify a definitive statement comparing their efficacy to that of the more conventional antihistamines. Some patients with particularly mild symptoms have used antihistamines only sporadically or have discontinued their use.

In two placebo-controlled studies from this center [4,5], disodium cromoglycate (400 to 800 mg/d) showed dramatic benefit for gastrointestinal symptoms, including abdominal pain, nausea, vomiting, and diarrhea. Individual patients have also noted clear-cut reduction of flushing, pruritus, urtication, headache, and cognitive and affective abnormalities. In the current series, 10 patients (seven of whom participated in the controlled assessments) have demonstrated symptomatic improvement on cromolyn therapy.

Among four patients treated with aspirin for pronounced flushing, one found it to be helpful and well tolerated, two noted definite amelioration of flushing but were unable to tolerate the esophagitis, gastritis, or duodenitis associated with the necessary doses (8 to 12 325-mg tablets per day), and one derived no benefit.

Ketotifen (6 mg/d) was used by two patients with marked flushing; both experienced significant benefit, and one also reports notable reduction of severe vascular-type headache.

One patient with severe esophagitis and gastritits/duodenitis has used omeprazole (60 mg/d) with pronounced benefit.

Prednisone at a chronic, low-dose (e.g., 10 mg), alternate-day dosage has been effective for maintenance of weight in one patient with severe malabsorption.

For cosmetic indications, several patients have requested therapy for the cutaneous manifestations of mastocytosis. Three patients in this series have had photochemotherapy with 8-methoxypsoralen and UV-A (PUVA) for urticaria pigmentosa. All have had appreciable improvement in the appearance of the eruption and amelioration of cutaneous symptoms. After PUVA, one patient with long-standing substantive, infiltrated papular and plaque-type lesions experienced not only fading but noteworthy diminution in the substance and infiltration of her lesions. Intralesional injection of triamcinolone acetonide was associated with resolution of individual lesions of urticaria pigmentosa in one patient but was considered an unacceptable means of addressing multiple lesions. Tunable dye laser therapy caused mild hypopigmentation and was unacceptable to the patient with TMEP and her family.

Avoidance of factors associated with exacerbations, e.g., extremes of temperature, stress, alcohol ingestion, and aspirin (in a minority of patients) have played a part in self-management. Frequent small feedings and vitamin, calorie, and protein nutritional supplementation have been used to treat malabsorption.

DISCUSSION

The observations detailed herein are based on a decade's clinical experience with systemic mastocytosis at a university-affiliated tertiary-care hospital ambulatory immunology center with a particular interest in this entity.

Controls and Comparisons The disadvantages of a retrospective approach are evident. Basing the selection of most laboratory tests and other investigations on perceived clinical utility to the individual patient may introduce a component of selection bias into estimation of the true incidence of various abnormal findings, inasmuch as more severely affected patients will be the more intensively and frequently studied. On the other hand, the absence of a well-defined protocol dictating observations to be made at specified intervals might also lead to failure to make observations that, although providing insight into the illness, might not come to mind as of value in routine clinical care. The initial observation of neuropsychiatric abnormalities in individual patients with mastocytosis led to the incorporation of electroencephalography, neuropsychologic testing, and psychiatric consultation into baseline evaluation. Interest in the possibility of peripheral as well as central nervous system involvement suggests that nerve conduction studies might reasonably be added to baseline evaluation. As a practical matter, our workup has become more standardized as retrospective evaluation has suggested areas for inquiry. With the evolution of this sort of standardized evaluation, of course, the development of control groups becomes more pressing.

Our current practice is to obtain bone-marrow aspirate and biopsy in all patients, both for baseline staging of the extent of involvement and to exclude the possibility of associated hematologic disease. All patients in the present series had not only clinical and histologic confirmation of the diagnosis of mastocytosis but also supportive biochemical evidence, organomegaly, or radiographic findings; in none of the patients reviewed is the diagnosis in doubt. We express the incidence of findings as that seen at some point during an extensive follow-up period, rather than the incidence at initial diagnosis.

Our figures suggest a somewhat younger population than the mean age of 59.5 years at diagnosis of systemic mastocytosis recently reported by Travis et al [1] for their large series of patients, but inasmuch as "age at diagnosis" in our group refers to diagnosis of any form of the disease, with diagnosis of systemic involvement generally coming some years later, the discordance is not so great as would initially appear. Other studies have related mean ages at diagnosis of systemic mastocytosis ranging from 48 to 71 years [6–9].

The interval between appearance of the eruption and diagnosis of urticaria pigmentosa varied greatly among patients, from almost simultaneously to several decades. The usual differential diagnoses appear to have been considered for these lesions (most often, freckles and nevi). Gastrointestinal and other extracutaneous symptoms in patients with urticaria pigmentosa were by no means immediately suspected to be associated with the cutaneous lesions. Indeed, in several instances years elapsed before such an association was considered.

The preponderance of female patients in the present series is in

contrast to most others, which have reported an equal sex ratio [7,8,10] or a slight male preponderance [1,6,9]. The explanation for our finding is not apparent, although it might be an artifact of referral patterns or of group size. The absence of any non-white patients from our series might reflect a lower incidence of mastocytosis, referral patterns to this center, the relatively greater difficulty of appreciating lesions of urticaria pigmentosa on dark skin, or diminished access to medical care of a relatively socioeconomically disadvantaged population.

The absence of a defined control population hampers any objective discussion of association of other diseases with mastocytosis. It is not clear that the incidence of hypertension (five patients) and ischemic heart disease with angina pectoris (four patients) is higher than would be expected in a closely followed population of the same size and age distributions. Some patients with systemic mastocytosis have an abnormal pre-beta lipoprotein, possibly associated with atherosclerosis and myocardial infarction [11]. Without an appropriate control population, however, the relationship between cardiovascular disease and mastocytosis, if any, remains unproved. The significance of a history of diverticulitis in four of our patients also requires comparison with an appropriate control group. Travis et al reported that two of 58 patients with systemic mast cell disease had a history of "diverticular disease of the colon" [1]. One patient in our series has osteogenesis imperfecta, and there is one previous report of focal mast cell infiltrates of bone marrow and urticaria pigmentosa in a patient with that rare disease [12]. Although rare familial cases of mastocytosis have been reported [10,13,14], none of our patients had a known family history of this illness.

Associated Hematologic Disorders Systemic mastocytosis has been associated with a variety of hematologic disorders [1,6–8,15–23]. In one series of 66 patients with systemic mast cell disease, 22 had some hematologic disorder: three with chronic myelomonocytic leukemia, seven with other dysmyelopoietic syndromes, five with myeloproliferative disorders, three with acute non-lymphocytic leukemia, one with chronic neutropenia, and three with malignant lymphoma [15]. Patients with systemic mast cell disease and an associated hematologic disorder had lower 5-year survival rates than did those with systemic mast cell disease alone. As a group, patients with an associated hematologic disorder were older, had increased likelihood of constitutional symptoms, anemia, leukocytosis, and pathologic fractures, and decreased likelihood of cutaneous symptoms, urticaria pigmentosa, or hepatomegaly.

In 1985, Horny et al [18] reviewed the histology of the bone marrow in systemic mastocytosis and drew prognostic implications based on three categories of marrow findings. However, Travis et al reported divergent associations in his study population [15]. Diffuse mast cell hyperplasia of the bone marrow also may occur in patients without evidence of systemic mastocytosis but with a variety of primary hematologic disorders, including pre-leukemic syndromes, acute leukemia, and lymphoproliferative disorders [24].

Several schemes for the classification of systemic mastocytosis have been proposed. One divides systemic (generalized) mastocytosis into benign and malignant categories, with a separate classification for mast cell sarcoma [23]. Travis et al suggested the categories of "indolent systemic mast cell disease," "systemic mast cell disease with associated hematologic disorder," "mast cell leukemia and mast cell sarcoma," and "aggressive non-leukemic systemic mast cell disease" [1]. Metcalfe and co-workers advanced a classification scheme using "indolent mastocytosis" (subclassified into overt cutaneous and systemic forms with further definition of the systemic category according to organ-system involvement and pattern of clinical presentation), "mastocytosis with associated hematologic dyscrasia" (subclassified according to the blood dyscrasia), "mast cell leukemia," and "lymphadenopathic mastocytosis with eosinophilia" [25,26].

At present no scheme is universally accepted. A classification of the disease as it presents in a given individual may eventually make reference not only to overt organ-system involvement as defined by clinical, histologic, and radiographic features, but also to mast cell morphology defined ultrastructurally, immunohistochemically, and functionally, and finally to the delineation of the responsible cytokines and growth factors. In the meantime, the scheme recently advanced by Metcalfe and co-workers is not only useful for comparison of subpopulations of patients with mastocytosis but also clinically relevant, inasmuch as the natural history and treatment of systemic mastocytosis with associated hematologic disorder are, in general, primarily determined by the hematologic dyscrasia. This classification may also indicate the direction of the work-up in particular patients, because the diagnosis of systemic mastocytosis may precede that of an associated hematologic disorder. Prospective evaluation of patients with systemic mastocytosis for hematologic disease—particularly, but not exclusively, those with suggestive factors, e.g., older age, constitutional symptoms, fractures, anemia, and absence of urticaria pigmentosa or hepatomegaly—may facilitate earlier diagnosis. The frequency with which such patients should be re-examined for manifestations of hematologic disorder after an initially negative work-up remains to be established.

Prognostic Factors There has been no mortality in our patient group thus far. All appear to belong to the category of benign indolent mastocytosis, and none has manifested evidence of emerging hematologic dyscrasia.

Indeed, the high incidence of urticaria pigmentosa and cutaneous symptoms, the significant incidence of hepatomegaly, and the relative paucity of constitutional symptoms, anemia, leukocytosis, and fractures are good prognostic features, suggesting a low incidence of associated hematologic disease [1,15], and the relatively large proportion of female patients is a favorable prognostic factor with regard to survival [1]. The most likely explanation for the occurrence of only indolent mastocytosis in patients seen at our center probably relates to referral patterns, particularly given our long-standing interest in dermatologic manifestations of this illness and the lack of a hematology-oriented physician among our investigators. The regional rather than national nature of our patient base may also mean that the less common forms of the disease, in particular sicker patients or those with more atypical presentations of systemic mast cell disease, are seen elsewhere.

A variety of solid tumors have occurred in individual patients with systemic mastocytosis, and their distribution appears to suggest no association with any particular type of tumor [16]. The overall rate of occurrence of solid tumors is not increased in the population of patients with systemic mastocytosis. Two of our patients (ages 73 and 82) had three solid malignancies (breast cancer in both and melanoma in one).

Symptoms Symptomatic manifestations of systemic mastocytosis are protean, and their intensity fluctuates over time in the same individual. Although flushing was almost universally noted, the patients' descriptions of the episodes ranged from almost an incidental finding to a major source of discomfort. Headaches with a description suggestive of a vascular etiology were a common complaint and also were variable in severity. Episodic vascular collapse was the most dramatic acute manifestation of systemic mastocytosis; although none of our patients have died from this cause, others have documented such mortality [27,28]. The lack of an association between mastocytosis and upper respiratory obstruction differentiates these episodes from the clinical entities grouped under the diagnosis of idiopathic anaphylaxis [29,30]. The usual absence of wheezing may be of some utility in differentiating mastocytosis from carcinoid syndrome, which also involves episodic flushing, hypotension, and gastrointestinal disturbance but apparently carries a higher incidence of bronchospasm [31,32].

Symptoms of rhinitis, reminiscent of perennial vasomotor rhinitis and not accompanied by ocular complaints, were reported by more than half of our patient group and were thus more common than the literature suggests [1].

Most of our patients noted pruritus and urtication but generally did not consider either a significant cause of discomfort. For unclear reasons, most patients in whom urticaria pigmentosa had remained constant or become more extensive, as well as those in whom the

lesions had become less prominent, recalled pruritus as having been more troublesome earlier in the course of their disease.

Gastrointestinal symptoms comprised the most distressing chronic complaints. The five patients with established diagnoses of frank ulcer or gastritis/duodenitis undoubtedly represent an underestimate of the true incidence of acid peptic disease, because many patients with suggestive symptoms were treated empirically and either did not have roentgenographic or endoscopic evaluation or were not evaluated before treatment. Our findings are in accord with those of a recent prospective study from the NIH [2]. Crampy, non-dyspeptic abdominal pain, showing a particular tendency to wax and wane, was also a common complaint. The dyspeptic pain may represent the consequence of acid hypersecretion, whereas the non-dyspeptic pain might be due to edema of the bowel wall consequent to local action of mast cell–derived mediators. One member of our patient group experienced replication of such symptoms with concurrent roentgenographic demonstration of small-bowel edema after alcohol ingestion [33]. Frequent bowel movements and occasional true diarrhea were a significant source of discomfort and inconvenience, as also reported by others [1,2].

Although documented cases of malabsorption have generally been mild [1,2,34–36], it was debilitating in one of our patients. The association of some degree of peripheral neuropathy with significant gastrointestinal mastocytosis in several of our patients suggests that failure to absorb adequate amounts of some substance may play a role in the development of neuropathy. An alternative explanation would be that peripheral neuropathy develops as a result of the influence of mast cells in perineurium of peripheral nerves. Although mast cell hyperplasia in that site has, to our knowledge, not been investigated in systemic mastocytosis, the mast cell has been implicated in the development of experimental allergic neuritis in rodents [37].

The occurrence of specific cognitive and affective abnormalities [3] may be the result of the same events that elicit chronic, recurrent headaches in patients with systemic mastocytosis. Either mast cell proliferation in the central nervous system or the pharmacologic action of mast cell–derived mediators acting at sites distant from those of their elaboration might be responsible. In normal human brain, mast cells are reported to be most numerous in the infundibulum, pineal, area postrema and choroid plexus, and the leptomeninges surrounding pineal and infundibulum and occasionally noted within supraoptic crest, subcornical organ, ventricles, and leptomeninges overlying other sites [38]. It has been suggested that mast cell–derived proteases may contribute to myelin damage in the peripheral and central nervous system [37,39]. To our knowledge, neuropathologic evaluation has not been performed in patients with mastocytosis, nor has the possible influence on the central nervous system of mast cell–derived substances generated at distant sites. The blood-brain barrier has been reported to be relatively impermeable to histamine [40]; however, a possible association between major depression and elevated salivary prostaglandin levels has recently been noted [41,42].

Antihistamines appear to have alleviated neuropsychiatric symptoms in some of our patients, but we have not performed a controlled study. Cromolyn sodium has been reported to be of benefit in individual patients [4], but no controlled studies specifically evaluating its neuropsychiatric benefit have been undertaken. A recent double-blind placebo-controlled study did not establish reduction of non-gastrointestinal symptoms at a level of statistical significance [5]. The occurrence of non-specific abnormalities on EEG of patients with systemic mastocytosis requires definition of a control group and possibly re-evaluation off medications. Further neurologic studies, including evoked potentials, brain electrical activity mapping study, and single photon-emission CT scan may be useful in determining regional variations in electrical activity and vascular supply.

Bone pain was a minor symptom in our patients and was poorly relieved by pharmacologic agents. Although several patients reported mild fatigue, constitutional symptoms were not prominent.

Clinically appreciable cutaneous lesions were noted in almost all patients. Of the three without clinically appreciable skin lesions, one had florid mast cell hyperplasia on biopsy of apparently normal skin, as has been reported elsewhere [43–45]. In no case was a diagnosis established on biopsy of clinically normal skin. The true incidence of systemic mastocytosis without appreciable skin lesions has not been established and may well vary with the category of systemic disease under consideration. A number of factors, including site selected, age, previous actinic damage, and inflammation due to other cutaneous conditions, have profound effects on cutaneous mast cell numbers, quantitatively more significant that the degree of increase in such numbers that has been documented in non-lesional skin [46–50]. Biopsy of non-lesional skin does not appear to be useful in either establishing or excluding the possibility of systemic mastocytosis. Lesions of urticaria pigmentosa may gradually progress or may fade with time despite persistence or increase in systemic symptoms. The development of a telangiectatic background in older individual lesions of urticaria pigmentosa may be caused by chronic local release of mediators with attendant vascular dilation and vascular damage. Resolution of urticaria pigmentosa has been associated with the development of hematologic dyscrasias in individual patients [25], but thus far we have not noted this association in our patients.

The incidence of organomegaly in our series falls within the range of values noted by others [1]. In our patients, organomegaly has generally occurred in those with a longer history of mastocytosis, and it seems likely that the composition of the series and the duration of the disease are the most important factors in determining the incidence of hepatosplenomegaly.

Laboratory evaluation has revealed anemia, generally mild, in four patients. Possible etiologies of such anemia include gastrointestinal blood loss, malabsorption of iron, folate, or other essential nutrients, or hematologic dyscrasia. In our patients, leukocyte counts and morphology were generally unremarkable. Eosinophilia has previously been reported in patients with systemic mastocytosis [1,51] and was present in five of our patients, in whom eosinophil counts appeared to increase gradually. Murine mast cells have been demonstrated to produce a number of cytokines, including the eosinophil growth factors IL-3, IL-5, and GM-CSF [52,53]. Persistent eosinophilia in a subset of patients with systemic mastocytosis may be an indication of functional diversity among mast cell populations of different individuals.

Routine chemistries revealed modest abnormalities of alkaline phosphatase in just over half of our patients, presumably from liver (in which mast cell hyperplasia and fibrosis, when present, are most prominent in the periportal region [54]), bone, or both. Modest elevations of SGOT, SGPT, and GTT also were frequent.

Two of 16 patients for whom data were available had IgG(k) monoclonal proteins on serum protein electrophoresis. The presence of oligoclonal immunoglobulin bands has been described in the setting of systemic mastocytosis [55]; it has been speculated that their presence might a) be due to a defect in the hematopoietic stem cell, causing both mastocytosis and "subclinical" myeloma; b) represent a humoral immune response to mastocytosis; or c) be due to mast cell elaboration of IL-6. The occurrence of small amounts of monoclonal immunoglobulins in two elderly patients in our series must be interpreted carefully, however, given the frequency of monoclonal gammopathy of uncertain significance in the general population, particularly in the elderly [56].

All patients in this study who had routine collection of 24-h urine for measurement of histamine had abnormal results on at least one occasion, and this appears to be a convenient test [57,58]. More specialized techniques for measurement of urinary histamine and its metabolites N-methylhistamine and M-methylimidizoleacetic acid are reported to be more sensitive, but their availability is limited [59–62]. Two of our patients who did have measurement of N-methylhistamine levels had results within a range reported to be highly associated with bone-marrow involvement [63] but have not had bone-marrow aspirates or biopsies. The repeated elevation of plasma histamine on successive measurements has been associated with increasing likelihood of the diagnosis of systemic mastocytosis

[64]. We did not routinely obtain that test, nor did we follow tryptase levels [65] during quiescent periods or flares of the disease.

The histology of lesions of urticaria pigmentosa was in no way different from the classic descriptions in the literature [66,67]. The histology of the cutaneous lesions in the patient with telangiectasia macularis eruptiva perstans was also as previously described [67]. Bone-marrow histology in our patients was similar to the type 1 form of marrow involvement described by Horny and co-workers (the most common presentation, characterized by focal mast cell infiltrates in paratrabecular and perivascular distribution, with bony trabecular thickening, fibrosis, scattered foci of lymphocytes, an eosinophilic surround, and normal hematopoiesis and normal fat in areas of bone marrow not involved with the focal mast cell aggregates [18]). In the two patients who underwent liver biopsy, findings were not suggestive of mastocytosis involvement [54]. No specimens of spleen or lymph node were examined pathologically; histologic findings in systemic mastocytosis involving these tissues have been described [68].

Findings on roentgenograms and bone scans in our patients were reflective of the literature [69–72].

Diagnosis The diagnosis of systemic mastocytosis should be considered after thorough history (with a mind to alternative diagnoses, for example, idiopathic anaphylaxis and carcinoid syndrome), physical examination, and evaluation of the results of laboratory studies. Biochemical evidence of mast cell involvement should be sought but is not in itself diagnostic or specific.

Demonstration of diagnostic lesions on histologic examination is central. If cutaneous lesions are present, skin biopsy is helpful in establishing the diagnosis. Bone marrow examination is appropriate in adult patients to establish systemic involvement and exclude associated hematologic disease. It should include both trephine core biopsy (to detect "classic" mast cell aggregates) and aspirate (which appears to reveal increased mast cell numbers in some patients in whom biopsies, at least when conventionally processed, are unremarkable). Plastic embedding of specimens seems preferable to routine processing.

Bone scan, other radiographic studies of bone, and contrast studies of the gastrointestinal tract may be useful in the individual patient, depending on the particular presentation.

Treatment In the absence of a more pathophysiologic approach, i.e., control of the mast cell hyperplasia, the treatment of patients with indolent mastocytosis is directed at the alleviation of symptoms and the prevention of complications. Agents that have proved useful in the chronic management of mastocytosis have included antihistamines, salicylates, cromolyn sodium, and ketotifen. Placebo-controlled studies of the efficacy of H1 or H2 antihistamines have not been performed; their efficacy is acknowledged by "clinical experience." The utility of cromolyn sodium in symptomatic amelioration, particularly with regard to gastrointestinal manifestations, has been addressed in several studies [4,5,73,74]. Salicylates have proved helpful in patients with flushing or with episodic vascular collapse [28]. Ketotifen has seemed useful in the small number of patients with flushing in whom we have used it. It has been demonstrated to reduce whealing and pruritus in urticaria pigmentosa [75], although a recent controlled comparison with hydroxyzine in pediatric cutaneous mastocytosis showed no advantage [76].

The platelet-activating factor antagonist BN52063 was reported to be useful in one patient [77], and terbutaline has been described as having possible therapeutic benefit [78]. Our experience has not extended to the use of either agent.

Prompt intervention with epinephrine and volume repletion is critical in mastocytosis-associated vascular collapse [79]. We have not documented any definite morbidity related to the use of beta-blockers, but the association of refractory anaphylaxis with their use [80] probably constitutes a relative contraindication in patients with systemic mastocytosis. PUVA appears an effective, although inconvenient, treatment for cutaneous manifestations [81–83] but is associated with increased risk of skin cancer.

The management of patients with systemic mastocytosis associated with significant hematologic disorders or more aggressive although non-malignant forms of the disease, does not come within the purview of this clinical summary, inasmuch as our experience has been limited to the indolent form of mastocytosis.

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ROUNDTABLE

DR. AUSTEN: For this group of patients with indolent mastocytosis, it was almost a decade until the diagnosis of UP was made, on the average. And then what was the interval between UP and development of systemic disease?

DR. HORAN: Well, I've presented data in terms of the interval from initial symptoms or signs to diagnosis of some form of mast cell disease, when the UP was recognized or the diagnosis of systemic mastocytosis was entertained. So the two numbers overlap to some extent. Your question, however, is the length of time between onset of the lesions on the skin and emergence of a syndrome recognizable as overtly "systemic." This was highly variable from patient to patient. Some had extracutaneous manifestations virtually simultaneous with the emergence of the eruptions, whereas in others the cutaneous eruption preceded systemic symptoms by decades.

The duration to a diagnosis of some form of mast cell disease was nine and a half years from onset of symptoms.

DR. AUSTEN: Okay. Clearly Dr. Horan spoke only about the indolent group. Over the past 20 years, our experience is probably 40 or thereabouts. But the point is that we believe the 21 that Dr. Horan talked about in detail are characteristic of the rest.

I would like to see several things commented on. For example, a negative bone-marrow biopsy in somebody who has classical disease in terms of flushing and even urine histamine. I'd like further discussion on intolerance. We find alcohol intolerance common and diagnostically useful and nonsteroidal anti-inflammatory drug intolerance of lesser value but quite informative.

Two patients clearly have the M spike; about a quarter have marked eosinophilia. We see no difference in the clinical course between those who have eosinophilia and those who don't and those who have M spikes and those who don't. What is your experience with bone pain in the indolent group? Finally, the neurologists and the psychiatrists feel very strongly that our patients have a very high incidence of a migraine-like vascular headache, very difficult to manage, with "an organic brain syndrome" but without organic disease.

DR. METCALFE: You see a spectrum of problems in mastocytosis much as we do, and I didn't see any glaring differences in the experience, other than what might be attributable to sampling. Our referral patterns do differ. Obviously we are often referred patients who are difficult to manage because, in some cases, the NIH is the "court of last resort."

We also see a high incidence—maybe 30% to 40%—of migraine headaches, or something that presents like a migraine headache. We also see alcohol intolerance. Non-steroidal anti-inflammatory drug intolerance is less frequent.

DR. KETTELHUT: Does the headache that you see in these adult patients correlate with the severity of their disease, or with their plasma histamine levels, or with any other known circulating mediator?

DR. HORAN: In general our mediator measurements are not adequate to address this issue.

DR. AUSTEN: The reason that a headache neurologist works with us is because we have not found a simple protocol that manages the headache problem in this group of patients. He has many different interventions, and he individualizes therapy.

DR. KETTELHUT: In our small series of 17 children, only two, about 10%, had headaches.

DR. SOTER: I see a high prevalence of headaches, on the order of 75%, in adults.

DR. AUSTEN: How about alcohol intolerance? Is it useful in clinical diagnosis?

DR. MINER: I think the single most valuable question you can ask is if a patient can tolerate red wine, because it contains alcohol, bisulfites, and tyramine. I would put alcohol intolerance very high on my history for these patients.

DR. METCALFE: I don't think the sulfites are an issue. We did a challenge study where we gave patients with mastocytosis or anaphylaxis, or both, reasonable amounts of sulfites. They had no problems. I would accept intolerance to alcohol in any form.

DR. AUSTEN: What's your feeling about the frequency of NSAID intolerance?

DR. ROBERTS: In the people we see, it's fairly low, probably somewhere around 3%.

DR. AUSTEN: All right. Thank you. M spikes.

DR. MINER: I'd like to comment on that. I have two patients who were referred for typical symptoms of mastocytosis. On GI biopsies both had increased plasma cells. I placed them on oral cromolyn and both of them responded in terms of their severe diarrhea and some of their other symptoms. Our pathologists can't explain the lesion in the GI tract.

DR. AUSTEN: Do you know anything more about our two patients in terms of their bone-marrow biopsies or hepatosplenomegaly?

DR. HORAN: They have hepatosplenomegaly. Their bone-marrow biopsies have shown focal mast cell accumulations and some fibrosis but haven't shown findings diagnostic of myeloma. Furthermore, the 21 patients reviewed have an average age of 57. Of the two patients with M spikes, one is in her early eighties, one in his early seventies. There could be individuals with benign gammopathy. We need to assess larger numbers of patients.

DR. PARKER: I don't recall seeing an M spike in any of the mastocytosis patients at NIH. Centers that have an interest in monoclonal gammopathies are reporting more and more individuals, particularly elderly ones, with M spikes. If it becomes a pattern in the mast cell patients, then maybe there's a connection. At this point I wouldn't try to read too much into two patients, one in the seventies, one in the eighties.

DR. AUSTEN: Okay. About a third of our patients have very striking eosinophilia. We can't relate it to anything else yet.

DR. METCALFE: We see eosinophilia more frequently in categories II and IV.

DR. KETTELHUT: When you look at the bone-marrow aspirates or biopsies on these patients, do you see an increase in eosinophils? And is that more indicative of systemic disease, or more aggressive disease?

DR. HORAN: Clinically, the patients with eosinophilia have not differed in any obvious way from those without eosinophilia.

DR. PARKER: The incidence of eosinophilia in your series is no different from what we've seen at NIH. Roughly, about 20% of the patients that we've seen have had eosinophilia. In what I call first-person series, by people who've seen the patients rather than going back through literature reviews, incidences range from 17 to 43%. The data correlating eosinophilia with other marrow findings are not readily available from the reports. But that whole issue is difficult because of the way people have defined patients; a lot of the series are restricted to patients with systemic disease, and they have to have marrow disease to fall into that category.

DR. SOTER: As a follow-up to that, other than Dr. Metcalfe's subset with eosinophilia, is there any prognostic information in the literature that these people with eosinophilia develop more severe disease?

DR. PARKER: No. Not that I've seen.

DR. AUSTEN: Yes, but the fascinating issue is that the eosinophils and the basophils may arise in the same colony-forming units. A basophil is not a mast cell. One of the more interesting issues is, why do you have eosinophilia with mast cells. Also, to the best of my knowledge, nobody has reported increased numbers of circulating basophils in mastocytosis, so that the association, I think, is very interesting. Thus, there appears to be a discrepancy between the clinical findings in this disease and the current dogma that basophils and eosinophils have a very close lineage.

DR. METCALFE: In all probability, we're seeing an expansion of the eosinophil lineage due to some specific cytokine that's eosinophil dependent. IL-5, for instance, is elevated in the plasma of some of our patients.

DR. SOTER: Do you think one reason your cutaneous responses on cromolyn didn't have any statistical significance is that only two itched and one had urtication—maybe there weren't enough for significance?

DR. HORAN: I think if we had had more patients and perhaps if we had followed them longer, the non-gastrointestinal symptoms would have reached a significant level, but that's speculation.

DR. KETTELHUT: Could you tell us more about the patients with the gastrointestinal symptoms as far as what sort of evaluation they had?

DR. HORAN: The seven patients who were from Brigham population had chronic, indolent, systemic mastocytosis as characterized in the discussion this morning. The GI symptoms were abdominal pain, cramping, nausea, vomiting, diarrhea, bloating. We did not do any prospective studies of these patients; in fact, we generally did not do anything other than follow symptoms. We did get urine histamines on a number of patients, to see whether there would be any changes. Of course, there had been no consistent changes seen in Dr. Soter's or in Dr. Metcalfe's papers, and we had too few samples for scientific assessment.

DR. KETTELHUT: Are you planning to do anything with these patients to see what disease they have in their gastrointestinal tract, if they have any mast cell infiltration. You've shown an improvement in these patients, and I was wondering what sort of pathology they showed on either endoscopy or biopsy or small bowel follow-through. Did they have any discernible pathology?

DR. HORAN: We have only done endoscopies when clinically indicated.

DR. AUSTEN: There's a historical point worth making. These folks were not selected because they had GI symptoms. They were simply part of the total group; except if they'd only had urticaria pigmentosa and no GI manifestations, I'm sure we wouldn't have used oral cromolyn sodium. They have indolent disease. We originally had statistically significant data when all symptoms and signs were analyzed together.

DR. KETTELHUT: It might be interesting to see if they have abnormal absorption. Maybe they are absorbing some of this oral cromolyn into their systemic circulation. Now that you've shown an effect, the question is, why are you having an effect? What is the role of oral cromolyn in improving the gastrointestinal symptoms in these patients?

DR. HORAN: That question hasn't been answered by any of the studies. It's a good one.

DR. ROBERTS: Has any study gone higher than 800 mg, except maybe in an occasional person?

DR. HORAN: A number of allergists apparently use cromolyn at higher doses. I've been told of physicians prescribing it at a dose of 1600 mg per day. I have one patient on 1200 mg per day at a greater benefit than at 800 mg per day. Interestingly, the majority of the patients in our recent study had been on 400 mg per day before entering the study. When they began to take 800 mg per day during the baseline period, they showed symptomatic improvement.

DR. ROBERTS: Clearly, one of the problems with this drug is that only a small fraction is absorbed. You are delivering a large amount to the GI tract, which may be why the GI symptoms show the most improvement. Has anybody tried spinhaling it into the lungs too, where, as I recall, twice as much is absorbed per dose as by mouth — or tried both routes to increase the systemic concentration?

DR. SOTER: We never had anyone breathe it.

DR. KETTELHUT: Are there studies on absorption in mastocytosis patients? Or are these in normals?

DR. AUSTEN: That's an interesting question. I don't think there are.

DR. MINER: At least in Crohn's disease, which has a lot of mast cells, you change permeability and you can measure that by lactulose or mannitol.

DR. AUSTEN: The suggestion is that either more is absorbed than we think or that the gut has some regulatory function in terms of the contribution of the gut mast cells to the total mast cell pool. Dr. Metcalfe, since you're interested in growth and development, what is your reaction?

DR. METCALFE: Some of you are familiar with the data from food-allergy studies where, if you challenge a person with something to which they're sensitive, macromolecules will go across the gut wall and enter the blood at a higher rate. So there does seem to be a so-called gatekeeper function of mast cells in the gut. Therefore, it's not unreasonable to ask if these patients absorb more cromolyn, and this might have something to do with its effect. There are even a few studies suggesting that treatment with oral cromolyn will shut down increased permeability when the mast cells are activated, which is a very attractive idea. To my knowledge, there are no studies with mastocytosis that look at blood levels of cromolyn or, in fact, assess permeability or assess whether, for example, it inhibits skin mast cells in mastocytosis patients. They are not inhibited by oral cromolyn in normal people, and cromolyn will not prevent anaphylaxis. As I read it now, putting everybody's data together, this is a drug that you would tend to give to patients with gastrointestinal symptoms. I think that treatment duration is important to mention here because, judging from the studies that you've reported, if you want to give cromolyn a therapeutic trial, then you have to be prepared to give it for many months.

DR. AUSTEN: And in fact, there is a wash-out effect, as Dr. Soter found 10 years ago.

DR. METCALFE: We do have to be careful of anecdotal reports of improvement. Mastocytosis is a disease of exacerbations and remissions. It is possible to draw the wrong inference from non-controlled studies.